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HEALTH EFFECTS OF ENVIRONMENTAL TOBACCO
SMOKE EXPOSURE IN OCCUPATIONAL ENVIRONMENTS:
A CRITICAL REVIEW OF THE LITERATURE RELATIVE TO
POTENTIALLY SUSCEPTIBLE OR SENSITIVE POPULATIONS

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INTRODUCTION

On September 20, 1991, the Occupational Safety and Health Administration (OSHA) issued a Request for Information seeking "comments and information on issues pertinent to indoor air quality (IAQ) in occupational environments" (Federal Register, 1991). Among the issues raised in the Request for Information is whether particular groups of individuals are more "susceptible" to adverse health effects from occupation exposure to environmental tobacco smoke (ETS) than are members of the general population.

In response to the Request for Information, this document provides a comprehensive review and analysis of the scientific literature assessing whether the "susceptible" groups suggested by OSHA suffer adverse health effects from short- or long-term occupational exposure to ETS. When relevant to this analysis, the scientific literature assessing whether the general population suffers adverse health effects from exposure to ETS also is evaluated. The following groups and health effects are addressed:

- I. individuals with pre-existing/underlying asthma, chronic obstructive pulmonary disease (COPD), and other chronic respiratory disorders, including acute and

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long-term effects of ETS exposure on the natural history of these diseases;

II. individuals with or without pre-existing/underlying ischemic heart disease and other chronic cardiovascular disorders, including acute and long-term effects of ETS exposure on the natural history of these diseases;

III. pregnant women, including the effects of ETS exposure on the mother, on pregnancy outcome and on the fetus/child;

IV. individuals claiming to suffer from so-called "multiple chemical sensitivities syndrome;"

V. individuals with atopic allergy;

VI. individuals with possibly heightened nonspecific (nonallergic) sensitivity to eye and/or upper respiratory irritation;

VII. individuals taking various therapeutic drugs and medications; and

VIII. elderly individuals.

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Because the Request for Information seeks comments with respect to IAQ in occupational environments, this review and analysis is limited primarily to issues potentially applicable to such environments and to populations potentially at risk from exposure in the workplace. Thus, issues affecting groups not likely to be exposed in occupational environments, such as children who are too young or elderly who are too old to work, or spouses not working outside of the home, are not addressed unless they are reasonably relevant to workplace exposure.

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I. INDIVIDUALS WITH PRE-EXISTING/UNDERLYING ASTHMA,
CHRONIC OBSTRUCTIVE PULMONARY DISEASE,
AND OTHER CHRONIC RESPIRATORY DISORDERS

Initially, it must be noted that, with regard to asthma, COPD and other chronic respiratory disorders, there are no published studies in the scientific medical literature and, thus, no data directly addressing workplace exposure to ETS. The validity of extrapolation of nonoccupational data to the workplace is questionable and studies specifically addressing workplace exposure clearly are needed.

A. Pre-existing/Underlying Asthma

One epidemiologic study addresses the effects of long-term ETS exposure on the respiratory system in asthmatic adults. Lebowitz (1984) reported the effects of several environmental factors on peak expiratory flow of adult asthmatics, including temperature, relative humidity, micropollen, indoor total suspended particulates (TSPs) and respirable suspended particulates (RSPs). He found that asthma attacks were related to temperature, indoor TSPs and RSPs, but observed no association between household smoking and peak flow or respiratory symptoms.

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A number of experimental studies have addressed possible acute effects of ETS exposure on respiratory parameters, including symptoms and pulmonary function. These generally have utilized a similar experimental design involving spirometric measurements obtained prior to, during and after exposure of subjects to machine-generated tobacco smoke in an exposure chamber. In addition, the participants in most cases have also provided subjective information on their perception of discomfort during these exposures. The levels of ETS to which these subjects have been exposed in these studies have been equal to or greater than the upper levels of ETS found in the most highly smoke-polluted real-life environments (such as pubs) and were generally much higher than levels of ETS found in typical office environments (Surgeon General, 1986; ? NRC, 1986; other citations to be inserted).

Under these conditions, exposure of nonasthmatic persons to ETS has been associated with such complaints as eye irritation, nasal discharge and/or stuffiness, cough, and unpleasant odor but most investigators have reported little or no acute effects on pulmonary function parameters, neither in such nonasthmatic individuals nor in nonasthmatic subjects who served as controls in studies looking at possible effects of acute ETS exposure on asthmatics (Shephard et al., 1979; Dahms et al., 1981; Wiedemann

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et al., 1986; other citations to be inserted). This has also been the case in studies in individuals subjectively claiming sensitivity to ETS and lower respiratory symptoms related to ETS exposure.

In a recent paper discussed in greater detail in the section on eye and upper respiratory irritation (Bascomb et al., 1991), it was reported that 15 minutes of exposure of nonasthmatic subjects to relatively high levels (45 ppm CO) of tobacco smoke in an exposure chamber resulted in small decrements (in the range of 2%) in such pulmonary function parameters as FVC, FEV₁, and FEF₂₅₋₇₅ in individuals with a history of smoke sensitivity (manifested by nasal symptoms of congestion, rhinorrhea or sneezing). Although the changes were statistically significant, they were clearly well within the range of reported intra-individual variation for these parameters (Bates, 1989; Miller, 1986) and, thus, of doubtful physiological significance, and, accordingly, were considered by the authors to be of no clinical significance. It should also be noted that, in view of the distinctive odor of tobacco smoke and the well-documented effects of odors, suggestion, and psychogenic factors on lower airway resistance (Shin & Williams, 19__; Luparello et al., 19__; other citations to be inserted), a psychogenically mediated basis for these very small decrements in respiratory flow rates in this study is highly plausible.

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Seven studies examining the effects of acute ETS exposure on asthmatics have been published in the peer-reviewed scientific literature (Table 1). While most of the studies reported eye irritation and, to a lesser extent, such symptoms as nasal discharge, shortness of breath, wheezing, and chest tightness as a result of high level ETS exposure in an exposure chamber, the reported objective effects of such ETS exposure on pulmonary function in asthmatics were more varied. Three of the studies reported no significant effects of ETS exposure on pulmonary function parameters (Shephard et al., 1979; Wiedemann et al., 1986; Jorres et al., 1990), while the other four reported significant decrements in pulmonary function in at least some of their subjects (Dahms et al., 1981; Knight and Breslin, 1985; Stankus & Lehrer, 1988; Stankus et al., 1988; Gurk et al., 1991).

Among the group of studies demonstrating pulmonary function decrements was the study by Stankus and associates (Stankus & Lehrer, 1988; Stankus et al., 1988). This study involved 21 asthmatic individuals subjected to a 2-hour exposure to machine-generated tobacco smoke in an exposure chamber that resulted in a CO level of 9 ppm, followed by an additional 2-hour exposure to a higher level of tobacco smoke (CO of 13 ppm) by those subjects who did not develop airflow obstruction at the lower level of exposure. Fourteen of the subjects, all of whom claimed a

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history of worsening asthma from exposure to ETS, exhibited no objective spirometric evidence of airflow obstruction at either level of tobacco smoke exposure, as did all of the nonasthmatic controls. Of the remaining seven asthmatic subjects, two developed significant decrements ($> 20\%$) in FEV_1 , FVC and peak expiratory flow at the lower level of smoke exposure (CO of 9 ppm), while five did so only at the higher level of smoke exposure (CO of 13 ppm). The authors could not demonstrate any significant correlations between claimed history of reaction to ETS and spirometric response, or IgE-RAST or pinprick skin test sensitivity to tobacco leaf, or smoke extract antigens, or between the serologic and skin immunologic tests and spirometric response to tobacco smoke challenge. They suggested that a "sensitive" subgroup of asthmatics who react with increased airflow obstruction to some component(s) of tobacco smoke might exist, with the mechanism of such "sensitivity" being other than immunologic but otherwise unknown.

Because of the distinctive odor of tobacco smoke, for which it is extremely difficult to control in such studies (citations to be inserted), as well as the well-documented role of odors, suggestion and psychogenic factors in the precipitation of airflow obstruction in asthmatics (Shin & Williams, 19__; Luparello et al., 19__; other citations to be inserted), a psychogenically mediated basis for the reductions in flow rates

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in such subjects remains highly plausible. Furthermore, data relating to variations in thresholds for nonspecific bronchial reactivity in asthmatics (citations to inserted) suggest that such nonimmunologic "hypersensitivity" may not be unique to tobacco smoke but, rather, may reflect a subset of asthmatic subjects with a lowered threshold for bronchial reactivity to a wide variety of nonspecific irritant and other stimuli, such as dust, particulates, fumes, gases, etc., as well as to specific (i.e., allergenic) stimuli, which may be encountered in both nonoccupational and occupational environments.

The study by Gurk et al. (1991), to date reported only in abstract, involved exposure of 20 patients reported to have asthma and 9 control subjects to "sidestream cigarette smoke" for 60 minutes in an environmental chamber, at tobacco smoke levels associated with 35-40 ppm CO. The report notes a "small but significant decrease of FEV₁" and a statistically significant increase in airway resistance (SRaw) among the asthmatic subjects but not in the controls. However, since the reported mean reduction in FEV₁ among the asthmatics appears to have been only 4% and the mean increase in SRaw only 13%, differences well within the range of reported normal intra-subject variability (Bates, 1989; Miller, 1986), these changes are of doubtful physiological significance, even if statistically significant. Because the abstract did not present sufficient methodologic

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details, the individual subject results, or other pertinent data, evaluation of the significance of this report and the validity of the authors' conclusions that "exposure to sidestream cigarette smoke may reduce lung function in sensitive asthmatics", if any, must await publication of the full paper with all of the relevant data.

The reason behind the discrepant results among the various experimental studies of asthmatics acutely exposed to ETS is unclear. It is unlikely, however, that intensity of ETS exposure is a factor. In fact, the ETS levels in the Wiedemann study (1986) were much higher than those estimated to be present in the Dahms (1981) and Stankus (1988) studies; yet, both symptoms and pulmonary function decrements occurred in some, if not all, of the asthmatics exposed to ETS in the latter two studies but not in the former study. It is also unlikely that the discrepancies reflect differences in "allergy" to tobacco smoke among the different study populations. As noted elsewhere in this document, the available data do not support an immunologic basis for reactions to ETS (Lehrer et al., 1986; other refs to be filled in), including airflow obstruction in asthmatics (Stankus et al., 1988). As noted above, Stankus et al. (1988) were unable to demonstrate any correlations between skin or serologic immunologic reactions to tobacco leaf or tobacco smoke extracts and decrements in airflow resulting from ETS exposure or

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subjects' perceived "sensitivity" to tobacco smoke.

Wiedemann et al. (1986) have suggested that the difference may lie in the severity of the asthma in the subjects at the time of the study, noting that their subjects had no asthmatic symptoms and were off medication while the subjects studied by Dahms et al. (1981) were taking medications and had pulmonary dysfunction even prior to ETS exposure. There is increasing evidence that asthma is an inflammatory condition, with the degree of bronchial reactivity to both specific and nonspecific stimuli related to the state of inflammation of the airways (citations to be inserted). It has been demonstrated that asthmatics whose condition is less well-controlled, i.e., who experience a more active inflammatory process in their airways, have a lower threshold for reactivity to a variety of nonspecific and specific stimuli than asthmatics whose condition is in a better state of control, either spontaneously or as a result of anti-inflammatory therapy (e.g., inhaled and/or systemic corticosteroids), and exhibit a higher threshold for precipitation of airflow obstruction by both specific (e.g., allergen) and nonspecific (e.g., irritant or cholinergic) stimuli (refs to be filled in).

It is, therefore, quite plausible that asthmatics whose condition is less well-controlled would have a lower threshold

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for bronchial reactivity to tobacco smoke, much as they have to other nonspecific (e.g., irritant) and specific (e.g., allergen) stimuli. Thus, the likelihood of a given individual with asthma developing airflow obstruction upon exposure to ETS would depend upon his or her particular threshold for bronchial reactivity to nonspecific stimuli at the time of exposure, which would, in turn, reflect the level of inflammation in his or her airways. The latter would be determined by the balance between the underlying state of the disease and the effects of any therapy, especially anti-inflammatory therapy. In this regard, it has been suggested that the continuation of asthma medication (bronchodilators and corticosteroids) on smoke challenge days in the study of Shephard et al. (1979) may have contributed to the negative results of that study (Lehrer et al., 1986).

It follows from the foregoing that workers with asthma whose condition is poorly controlled might be more "sensitive" not only to ETS but to other specific (e.g., allergen) and nonspecific (e.g., dust, chemicals, other irritants) stimuli that they might encounter in the workplace (as well as in other settings), even in a smoke-free environment. Because it is impossible to provide a workplace totally free of all, or even most, potentially bronchoprovocative stimuli for such individuals (who likely represent only a small proportion of asthmatics in the work force), it makes more sense to concentrate on controlling their

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asthma rather than attempt to accomplish such a task.

It is also possible that the responses to experimental ETS exposure noted in some asthmatics in these studies, as well as the subjective reports by some asthmatics of exacerbation of their asthma upon exposure to ETS, reflect psychogenic factors rather than a physiological reaction to ETS. Suggestion, other psychogenic influences and odors have been well documented to cause increased airflow obstruction, including the precipitation of full-blown clinical episodes, in asthmatics (citations to be inserted) and to affect pulmonary function in some nonasthmatics (Knapp and Mathe; 1985; Kotses, et al., 1987; Shin and Williams, 1986). Since it is virtually impossible to disguise the odor of tobacco smoke, which has an extremely low threshold for perception (Nishida et al., 1990; other citations to be inserted), most likely the subjects in these studies were able to differentiate between ETS and control exposures. Furthermore, as discussed elsewhere in this document, because the threshold for odor detection is considerably below that for irritation (citations to be inserted), subjects may have perceived an odor at very low levels without even having been consciously aware of this perception. An individual anticipating an adverse reaction to ETS may very well have such a reaction on a psychogenic basis upon detecting the distinctive odor of tobacco smoke.

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In addition, there were variations among the experimental studies in the degree of stress associated with each procedure and in other factors that may have resulted in a greater or lesser degree of awareness or perception of tobacco smoke exposure. For example, the design of the Dahms et al. (1981) and Stankus et al. (1988) studies did not include a control period in the chamber during which there was no exposure to tobacco smoke. Therefore, it is quite possible that the pulmonary function changes they observed were due, at least in part, to anxiety and other psychological factors associated with the testing conditions (such as confinement, frequent spirometric testing and blood sampling and emotional reactions to tobacco smoke odors). Five of the 7 smoke sensitive subjects in the Stankus study (1988) required confinement in a smoking chamber for up to 4 hours before exhibiting a decrement in respiratory flow rates. While this represented a greater degree of exposure (both higher levels and longer duration) to tobacco smoke, it could also have reflected the increased stress of the procedure.

In the Knight and Breslin (1985) study, where adverse pulmonary effects were reported, control exposures always occurred on the day preceding smoke exposure, in contrast to the random exposure protocol in the negative study of Shephard and co-workers (1979). When control and experimental exposures are not randomized, the possibility increases that anxiety and other

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psychogenic factors will have caused the reported effects.

Weidemann et al. (1986) provided their subjects with goggles to prevent eye irritation. This was not done in any of the studies reporting adverse effects of ETS exposure on pulmonary function in asthmatics. The goggles, by reducing eye irritation, may very well have reduced also some of the psychogenic influences associated with experimental tobacco smoke exposure and the perception of tobacco smoke exposure. A report (McKay et al., 1989) of a single case study of an individual who exhibited intense physiological reactions (such as tachypnea, tachycardia, copious sweating, coughing, vomiting, shortness of breath and chest tightness) to brief exposures (5 min) to smoke from a single cigarette, without associated changes in pulmonary function, is suggestive of a significant role for psychogenic factors in such reactions.

Another study (Urch et al., 1988) attempted to determine whether ETS effects on asthmatic (and nonasthmatic) subjects could be due to suggestibility. "Suggestibility," defined by the authors as reflecting hypochondriasis, depression, or hysteria in subjects, was determined by a variety of personality profile tests and the diluent/air FEV₁ ratio, i.e., the ratio of the FEV₁ following exposure to the methacholine diluent (phenol-buffered saline) relative to the ratio of the same following exposure to

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air prior to the subsequent methacholine inhalation challenge. Subjects were told that methacholine could produce wheezing and/or shortness of breath and a low diluent/air FEV₁ ratio was regarded as a physiological indicator of suggestibility. Subjects were randomly confined for 65 minutes to an exposure chamber under each of the following conditions: 1) room air alone, with tobacco smoke visualized but not smelled; 2) low (17 ppm CO) tobacco smoke exposure; and 3) high (31 ppm CO) tobacco smoke exposure. The authors reported significant dose-response relationships between the levels of tobacco smoke exposure and symptoms (such as unpleasant odor, eye irritation, sore/dry throat, and nasal stuffiness), nasal airflow resistance and decrements in pulmonary function. Despite noting significant correlations between suggestibility (both psychologically and physiologically determined) and responsiveness to ETS, the authors concluded that suggestibility had, at best, a weak influence on the physiological effects of ETS exposure. This conclusion was based primarily on the assumption that psychological factors could not explain the dose-response associations that were observed.

The validity of this assumption remains to be determined, however, as there is no basis to assume that gradations of perceived discomfort (e.g., odor, eye irritation, nasal congestion) do not occur and cannot, in turn, produce

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proportionate psychogenically-mediated changes in respiratory flow rates. Furthermore, while the authors reported a statistically significant dose-response relationship between respiratory parameters (FVC and FEV₁) and ambient levels of CO, they did not note a statistically significant overall association between tobacco smoke exposure and the occurrence of decrements in these respiratory parameters, a weakness in the data that makes the assumption of an unlikely psychogenic effect even less appropriate.

Four studies have examined bronchial reactivity before and after smoke exposure. The data to date are inconsistent and contradictory (Table 1). Knight and Breslin (1985) noted increased bronchial reactivity to histamine challenge after smoke exposure. Gurk et al. (1991) reported no change in bronchial reactivity to methacholine after tobacco smoke exposure in their asthmatic group as a whole but noted a "small increase" in such reactivity in a subgroup of asthmatics who had a greater than 5% decrease in FEV₁ following smoke exposure. Wiedemann et al. (1986) reported an opposite effect -- a decrease in bronchial reactivity to methacholine challenge after smoke exposure. Jorres et al. (1990) reported no effect by experimental smoke exposure on bronchial reactivity to methacholine provocation.

The reasons for these differences are unclear. They could

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reflect, in part, differences in the bronchoprovocative agents used, the challenge methodology, the underlying state of airway inflammation, the use of bronchodilator and anti-inflammatory medication, and other factors that have been noted to affect bronchial reactivity (Sparrow et al., 1987; Sparrow et al., 1991; O'Connor et al., 1989; Cerveri et al., 1989; Bates, 1989; Miller, 1986; Hargreave & Ramsdale, 1988).

In summary, the epidemiological data with respect to long-term effects of ETS exposure on adult asthmatics are quite limited and inconclusive and do not support a finding of an association between exposure and adverse effects. Similarly, the somewhat larger (although still relatively few) number of experimental studies of acute effects of ETS exposure in asthmatic adults that have been done have produced contradictory and equally inconclusive results. While it appears that a small subset of individuals with asthma may react adversely to ETS exposure with worsening of respiratory flow rates and, in some cases, even clinical exacerbations of their disease, the reasons for these reactions remain to be determined. Likely reasons include poor control of asthma, with increased airway inflammation resulting in a lowered threshold for bronchial reactivity not only to tobacco smoke but to a large variety of specific and nonspecific stimuli as well, and a psychogenically-mediated reaction. These are not mutually exclusive. In any

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event there is no evidence that such exacerbations, whatever their reasons, result in any long-term effects or alter the course of the disease.

Irrespective of the reasons, as far as the workplace is concerned, the problem would be more appropriately and effectively addressed by improving control of the underlying asthma in individual patients -- specifically by a more aggressive use of anti-inflammatory medication (such as inhaled corticosteroids, which are associated with minimal side effects) -- rather than by attempting the probably impossible task of making the workplace totally free of all potential specific and nonspecific bronchoprovocative stimuli.

B. COPD and Other Chronic Respiratory Disorders

The data with respect to potential effects of both short-term and long-term exposure to ETS on COPD and other chronic respiratory disorders, for all practical purposes, are virtually nonexistent (Surgeon General, 1986; NRC/NAS, 1986). A recent epidemiologic study from Poland assessing the effects of domestic cooking on chest diseases and respiratory problems of elderly women reported a weak association between ETS exposure and the symptom of shortness of breath, but not chronic cough or chronic phlegm (Jedrychowski et al., 1990 a & b). The authors also

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reported an association between ETS exposure and FVC and FEV₁ among women who cooked for more than 2 hours per day but not among women who cooked less than 2 hours per day or in the group as a whole. The significance of these findings is uncertain because the reported associations are weak and the control of various potential confounding variables such as socioeconomic status, housing, household crowding, other exposures, other medical conditions (e.g., cardiovascular disease), etc., is questionable. Also, internal inconsistencies in the data raise questions about their validity and significance.

Individuals with cystic fibrosis have chronic pulmonary disease. Although primarily a childhood disorder, improved management in recent years has permitted a limited number of these patients to live to adulthood and enter the work force (citations to be inserted). A few epidemiological studies have attempted to assess whether ETS exposure adversely affects patients with this disorder. These studies, however, exclusively address the pediatric age group and the results are inconclusive. Campbell et al. (1991) reported that, in a subset of cystic fibrosis patients with a homozygous delta F 508 deletion, heavy household smoking (3-4 packs/day) was associated with lower FEV₁ and Schwachman score after correcting for socioeconomic status. On the other hand, Rubin et al. (1990) reported no association between the number of cigarettes consumed daily in the home and

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respiratory symptoms and most pulmonary measurements in children with this disease. Similar results were also reported by Gilljam et al. (1990).

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TABLE 1. EFFECTS OF ACUTE EXPERIMENTAL TOBACCO SMOKE
EXPOSURE ON PULMONARY FUNCTION IN ASTHMATIC ADULTS

<u>STUDY</u>	<u>FINDINGS</u>
Shephard, et al., 1979b	No effects on pulmonary function; eye irritation and to a lesser extent symptoms such as nasal discharge, wheezing, and chest tightness reported
Dahms, et al., 1981	Linear, time-dependent decr. in FVC, FEV ₁ , FEF ₂₅₋₇₅ ; incr. symptoms
Knight/Breslin, 1985	Decr. pulmonary function; incr. symptoms (eye irritation, chest tightness, wheezing); incr. sensitivity to histamine challenge
Wiedemann, et al., 1986	No effects on baseline pulmonary function; eye irritation (before goggles), nasopharyngeal irritation, mild cough; decr. sensitivity of methacholine challenge
Stankus, et al., 1988	Decr. (>20%) in FEV ₁ in 7 of 21 subjects; Eye irritation in all subjects; nasal congestion in some subjects; cough, shortness of breath and/or chest tightness in all subjects showing physiological responses to ETS

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Table (continued)

Jorres et al., 1990 (abstract)	No effects on pulmonary function and bronchial responsiveness to methacholine challenge; eye irritation was only symptom
Gurk et al., 1991 (abstract)	4% decr. in mean FEV ₁ ; 13% incr. in mean SRaw; no change bronchial reac. to methacholine in asthmatics as a group; small incr. bronch. reac. in subgroup of asthmatics with >5% decr. FEV ₁

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II. INDIVIDUALS WITH AND WITHOUT PRE-EXISTING ISCHEMIC HEART
DISEASE AND OTHER CHRONIC CARDIOVASCULAR DISORDERS

A. Individuals with Pre-existing Conditions

The question ~~of~~ whether ETS increases the risk of death from cardiovascular disease in susceptible populations is relevant because ETS contains carbon monoxide (CO), to which, it might be surmised¹ an individual with an ischemic heart condition would be quite sensitive.

The Committee on Passive Smoking, Board on Environmental Studies and Toxicology, National Research Council (NRC, 1986) evaluated ten experimental studies (i.e., in controlled chambers) and six observational studies which attempted to measure carboxyhemoglobin (COHb) levels in ETS-exposed non-smokers. In nine of the experimental studies, exposures ranged from 3.1 to 15.1 cigarettes/hr/10 m³; chamber CO levels ranged from 4.5 to 20 ppm; control COHb levels ranged from 0.3 to 2.0%; changes ranged from 0 to 1.2 % COHb; and post-exposure COHb levels ranged from 0.3 to 2.6%. The magnitude of the changes suggested no obvious correlation with control COHb or with number of cigarettes burned. In one of the experimental studies, in which 50 cigarettes/hr/10 m³ were burned, chamber CO level was 90 ppm and the COHb level increased from a pre-exposure value of 2% to a

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level of 5%. In the observational studies (flight attendants; pub; restaurant; office; self-reported), no significant differences in COHb between exposed and non-exposed individuals were reported (nonexposed, 0.9 to 2.3%; exposed, 0.8 to 2.3%). Therefore, except for one chamber study in which an unrealistically high number of cigarettes were burned and an unrealistically high level of CO was produced, the data do not support a finding that ETS exposure results in a physiologically significant effect on COHb levels.

To our knowledge, only three studies have attempted to assess the effects of ETS exposure in individuals with pre-existing cardiovascular disease who might be, thus, susceptible to any adverse cardiovascular effects of such exposure. Aronow (1978) reported that non-smoking angina patients experimentally exposed to ETS experienced significant increases in systolic blood pressure and heart rate and decreases in time to onset of angina. Coodley (1978), Robinson (1978), Waite (1978) and Wakehan (1978) criticized the study for its subjectivity (e.g. the evaluator of the angina who reported anginal symptoms was not blinded) and lack of control for obscured factors (e.g. stress). Furthermore, although not related specifically to this study, Aronow was barred from performing government-sponsored studies because of scientific misconduct (Budiansky, 1978), and, for this reason, the NRC committee (NRC, 1986) and the Surgeon General

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(1986) attached little, if any, weight to it in their reports.

In a Russian study of the effect of ETS exposure on cardiovascular disease susceptible individuals (Khalfen and Klochkov, 1987), normal individuals and subjects with ischemic heart disease were given a physical stress tolerance bicycle ergometer test. The authors used a continuous workload, in steps of 3-min duration, with 25 watt increases in power. The test was terminated if one of the following occurred: submaximal pulse rate; horizontal and downsloping displacement of the ST segment by 1 mm or more below baseline; a typical angina episode arrested by taking nitroglycerin; or T-wave inversion in two or more leads. Results were noted and, after a 2-hr stay in an ETS atmosphere, the test was re-administered. Normal individuals showed no change in physical stress tolerance. In contrast, patients with ischemic heart disease were reported to show a significant decrease in such tolerance. The authors claimed that these results were obtained whether or not the room was "ventilated"; however, the "ventilation" consisted of turning on a fan for 10 minutes at the end of each hour, which obviously was not true ventilation because no air exchange took place. Under the conditions of the study, fifteen subjects were maintained in a 76.8 m³ room, which was apparently unventilated, for 2 hours. This, along with the displacing effects of ETS, raises the question of whether a reduced oxygen level affected the patients.

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Similarly, the effect of increased carbon dioxide levels requires consideration. Also, no measurements of air quality or COHb were reported and, finally, one of the criteria for terminating the ergometer test was the occurrence of angina but the number of tests terminated on this basis was not reported. The problems with interpretation of angina for the Aronow (1978) study also apply here.

A third study addressing, in part, whether ETS had an effect on cardiovascular disease susceptible individuals was recently reported by Leone et al. (1991). This study also relied upon a bicycle ergometer as a test for exercise stress tolerance. Two groups of patients were studied, one with no history of cardiovascular disease and another comprised of survivors of myocardial infarctions, first in a normal atmosphere and subsequently in an atmosphere in which 15 to 20 cigarettes were burned within 30 minutes in order to obtain a carbon monoxide atmosphere of 30 to 35 ppm. The first group showed no change in exercise tolerance due to ETS exposure but the infarction survivors showed a statistically significant reduction in peak exercise power and an increase in time to recovery of pre-exercise heart rate. The interpretation of this apparent effect of ETS exposure, however, is confused by group characteristics and responses. The history negative group was significantly younger (30.5 ± 8.5 yr; range 17 to 44 yr) than the infarction

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survivors (53.8 ± 5.3 yr; range 43 to 59 yr); additionally, while the infarction survivor group showed an increase in COHb during exercise in the ETS environment (from $1.2 \pm 0.16\%$ to $2.3 \pm 0.40\%$), the history negative group did not (from $1.4 \pm 0.20\%$ to $1.7 \pm 0.40\%$). Thus, as the authors suggested, the difference in COHb might be age-related. The questions raised by this study invalidate any causal inference that might be made from the data at first glance.

An additional question raised by the Leone *et al.* study is whether carbon monoxide was the real cause of the exercise stress intolerance of the infarction survivors. A logical extension of this question is whether the history negative group would have experienced the exercise intolerance had the COHb been the same. The answer is not obvious. In the Khalfen and Klochkov (1987) study cited above, no changes were observed in healthy individuals. On the other hand, McMurray *et al.* (1985) concluded that ETS exposure affects exercise performance in females, although some of the changes reported were very small and of doubtful physiological significance. For example, ETS reduced the duration of exercise treadmill from 25.75 ± 0.85 min to 23.63 ± 1.16 min and the rating of perceived exertion at the end of the control trials averaged 16.5 ± 0.6 units and was significantly increased to 17.4 ± 0.6 units during the ETS exposure. In addition, the authors reported that the "post exercise venous

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blood lactates averaged 6.8 mM during the smoke trials [,] significantly greater than the controls (5.5 mM)" but failed to give any indication of the variance or whether "significantly" means $p < 0.05$, which does not seem likely without information on variance.

B. Individuals Without Pre-existing Conditions

Little, if any, further information exists addressing the response of susceptible groups to the potential cardiovascular effects of ETS exposure. Therefore, it is important to look at the issue from the perspective of all groups. Certainly if the healthy population is affected an increased sensitivity of the "susceptible" population can be presumed. In this regard, one must ~~to~~ examine the review and analysis by Glantz and Parmley (1991a) which, due to promotional efforts (citations to be inserted - e.g., Newsweek, etc.), has become the focus of the discussion of putative cardiovascular health risks from ETS exposure.

Glantz and Parmley (1991a) provide a risk analysis estimating 37,000 deaths from ETS-related heart disease annually. The authors, however, not only fail to look for refuting data, they do not even consider such data already available to them. This violates one of the most basic tenets of science, namely

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that, since refutation has such a more potent influence on evaluating a hypothesis than does verification (corroboration), hypothesis testing should favor attempts at refutation (citation to be inserted - Rothman causation book).

For example, in their discussion of the Aronow (1978), Khalfen and Klockov (1987), and McDonald et al. (1985) studies, the authors ignore anything that refutes or could refute a causal relationship between ETS and cardiovascular disease. Further, the authors use a meta-analysis of the epidemiological data to arrive at their positive association between ETS exposure and cardiovascular disease but fail to discuss the pitfalls of the use of meta-analysis (Fleiss & Gross, 1991; Chalmers, 19__; other citations to be inserted). Huber and Brockie (1991) criticize^d this failure; Glantz and Parmley's response, essentially, was to take refuge in the fact that the editors and reviewers of Circulation determined their manuscript worthy of publication (Glantz and Parmley, 1991b). However, they failed to acknowledge^{e/} that editors and reviewers rarely, if ever, have an encyclopedic command of the literature cited by the authors of a submitted manuscript. The presumption of candor is always made, and when it is not afforded, deceptive analysis -- intentional or not -- can only be detected over a period of time after the publication of a manuscript. The deceptions of people such as John Darsee and William Summerlin -- and Wilbert Aronow himself -- all became

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known after extensive publication of their work, which, in manuscript form, was approved by some of the best scientific journals in the world.

Three of the four epidemiologic studies in men and five of eight in women cited by Glantz and Parmley failed to find a statistically significant increase of heart disease associated with ETS exposure. This raises three points: (1) a causal inference must be based on something other than a statistical association; (2) there must be some plausible reason for the sex differences and the inter-study differences; and (3) by globally considering all of the studies, without breaking out inconsistencies, Glantz and Parmley precluded critical evaluating information from reaching the reader.

Glantz and Parmley point out that the epidemiology data analyzed in their paper was based on exposure to ETS at home. They then assert that

Household exposures to ETS at home are generally much smaller than exposures at work, where density of smokers is generally higher. As a result, these studies generally underestimate the risk and attendant public health burden due to ETS - induced heart

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disease. Kawachi et al adjusted Wells' relative risk to account for workplace exposures to ETS and found that the relative risk increases 2.3 (95% CI, 1.4-3.4) for men and 1.9 (95% CI, 1.4-2.5) for women. Thus, any potential confounding of the results because of exposure to ETS outside the home will tend to produce underestimates rather than overestimates of the effect of ETS. Likewise, estimates of public health impact based on risks computed from household exposures will be lower than the true public health impact.

Conflicting with these conclusions are the recent findings of Dobson et al. (1991) on ETS exposure at work and risk of heart attack or coronary death. In male non-smokers, the odds ratio for risk of heart attack or coronary death was 0.95 (95% CI, 0.51-1.78). In female non-smokers, the odds ratio for risk of heart attack or coronary death was 0.66 (95% CI, 0.17-2.62). This suggests that ETS exposure at work is not associated with increased risk. Indeed, the data obtained for women indicates decreased risk.

Glantz and Parmley also claim that "five studies have ...

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suggested an increase in the risk of non-fatal coronary symptoms, including angina and myocardial infarction." A subsequently published study addressing cardiovascular effects of active smoking does not support their view. Seltzer (1991) concludes:

as a result of more complete analysis of available Framingham Heart Study data on the association of cigarette smoking to incidence of uncomplicated angina pectoris than has previously been published in Framingham papers, it was determined that there is consistently negative risk factor association for women at every follow-up period from 12-30 years, with Framingham women cigarette smokers experiencing 30-40% lower rates of uncomplicated angina pectoris than non-smokers, the rates also declining with increasing amounts of cigarettes smoked.

In comparing the putative risks of developing heart disease from ETS versus developing cancer from ETS, one point emerges that defies logic. The relative risk of death due to cancer in ETS-exposed individuals is about 2 in one study (Mantel, 1986), and is stated by Glantz and Parmley (1991a) to be 1.3. But Glantz and Parmley (1991a) also report the relative risk of heart

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disease death from ETS to be 1.3. On the other hand, the relative risk of cancer from active smoking is around 10 and the relative risk of death due to ischemic heart disease as reported by Hole et al. (1989) is 2.27 in active smokers and 2.01 for individuals exposed to ETS. Glantz and Parmley fail to explain how the ratio of death risks between active smoking and ETS exposure for cancer is 10 to 2 or 10 to 1.3, while the ratio of death risks between active smoking and ETS exposure for heart disease can be 2.27 to 2.01 or 2.27 to 1.3.

In linking ETS to heart disease, Glantz and Parmley emphasize that cigarette smoke can cause platelet aggregation but cite only studies that support their argument and exclude acute changes in platelet function during smoking (Circulation 66:44, 1982; Adv Prostagland Thromb Leuk Res 11:359, 1983 - authors to be inserted and form of citation corrected). They also exclude a study demonstrating that the major nicotine metabolite, cotinine, stimulates synthesis of prostacyclin (Prostagland Leuk Essent Fatty Acids 40:261, 1990 - authors to be inserted and form of citation corrected), a platelet anti-aggregant factor.

Glantz and Parmley also stress the role of polycyclic aromatic hydrocarbons (PAHs) in accelerating the development of atherosclerosis. Their thesis is that PAHs can be atherogenic by increasing the volume of the plaque and by acting as a mitogen

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similar to that released by activated platelets to stimulate division of aortic smooth muscle. It is doubtful, however, that the level of PAHs achieved from ETS would be high enough to be atherogenic. Indeed, it recently was reported that the level of PAHs achieved with ETS is insufficient to induce hepatic microsomal oxidative p-450 enzymes (Casto et al, 1990). The findings in this study are quite significant because they were obtained in an environment where the tobacco smoke pollution was described as "very heavy."

The point is that Glantz and Parmley (1991a) cannot be considered to have established causation because they applied a "scientific" methodology that considers only hypothesis verification and ignores hypothesis refutation. Quite frankly, in this regard their paper is deceptive. Though the deception may be unintentional, Glantz and Parmley (1991b,c) are explicit in their contentions that tobacco industry-supported scientists cannot be trusted either for their research results or opinions and that the efforts to eliminate smoking requiring the tactics of "guerilla warfare" (Glantz, 1988).

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III. PREGNANT WOMEN

In considering the potential effects of occupational exposure to ETS on pregnant women, it is necessary to examine both the pregnant worker herself and the fetus. As discussed in the literature review below, no evidence exists that a pregnant worker is any more susceptible than a non-pregnant worker to any irritant, respiratory or cardiovascular effect of ETS. Furthermore, epidemiologic studies provide no basis for the conclusion that the fetus is at risk from the mother's exposure to ETS.

A. Pregnant Workers as a Susceptible Population

OSHA cites Calabrese (1978) as the basis for its concern that there may be increased sensitivity to environmental pollutants during pregnancy. The concerns raised by the author, however, are mostly theoretical. He merely suggests that, "[a]s a result of the numerous physiological modifications which the pregnant woman must experience, there exists the possibility that she will respond differently to environmental stressors."

With respect to respiratory effects of ETS, there is no basis for expecting, nor data demonstrating, that pregnant women have increased airway responsiveness. This applies to the

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nonspecific irritant response by women in general and by women with asthma. In fact, during pregnancy the airways might even be less responsive due to the smooth muscle relaxing activity of progesterone, which is present at increased concentrations. This is thought to account for the reduced pulmonary resistance and increased airway conductance associated with pregnancy (Gee et al., 1967).

During pregnancy changes occur in endogenous carbon monoxide production and red blood cell mass (Longo, 1977) that could, theoretically, affect the response to ETS exposure. Stetson and Andrasik (1984) compared pregnant and non-pregnant smokers with respect to the change in carboxyhemoglobin (COHb) concentration and pulse rate associated with active smoking. The act of smoking was standardized in order to equalize, to the extent possible, the delivered doses of nicotine and carbon monoxide. The baseline COHb concentration in pregnant women was found to be the same as in non-pregnant women, as was the increase in COHb measured after smoking. The magnitude of the increase in pulse rate measured after smoking was also the same in pregnant and non-pregnant smokers. Given the lack of effect of pregnancy on the acute response to active smoking, it is highly unlikely that the pregnant woman would be more susceptible to any acute cardiovascular effect of ETS exposure.

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B. Fetuses as a Susceptible Population

In the literature addressing the effects of ETS exposure on the fetus, there has been some semantic confusion in the use of the term "passive smoking." Some have used this term when referring to the fetus of a mother who is an active smoker. In any event, this is not the issue here; in keeping with the charge of the Request for Information, this review considers relationships between a non-smoking mother's exposure to ETS and pregnancy outcome and risk of cancer.

Components of ETS breathed by the pregnant woman that are absorbed into her blood stream are expected to reach the fetus if they are lipid soluble and can cross the placental barrier and are first not metabolized and/or eliminated by the mother. It is not surprising, therefore, that biomarkers of tobacco smoke exposure, including carboxyhemoglobin, thiocyanate and cotinine, have been found in amniotic fluid, umbilical cord blood and urine of newborns of both smoking and non-smoking mothers (Bottoms et al., 1982, Luck et al., 1985; Etzel et al., 1985; Jordanov, 1990; Oryszczyn et al., 1991). Some studies have reported a significantly higher concentration of tobacco smoke biomarkers in nonsmokers exposed to ETS as compared to nonsmokers with no ETS exposure (Bottoms et al., 1982; Jordanov, 1990; Oryszczyn et al., 1991); others have not (Sorsa and Husgafvel-Pursiainen, 1988;

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Hauth et al., 1984). In any case, biomarker studies confirm that the fetal exposure to tobacco smoke constituents following maternal exposure to ETS is considerably less than that following active smoking by the mother.

The potential effects of maternal exposure to ETS on the fetus fall into two general categories: (1) the potential effect on pregnancy outcome, i.e., intrauterine death or stillbirth, prematurity, or intrauterine growth retardation; and (2) the possibility that fetal exposure could increase the risk of birth defects or cancer later in life.

Pregnancy outcome: Epidemiologic studies. Epidemiologic studies of pregnancy outcome measure such endpoints as incidence of spontaneous abortion, late fetal death or stillbirth, prematurity, and low birth weight. Of these outcomes, the association between active smoking by the mother and low birth weight is the strongest. For this reason, it has been the endpoint focused upon in most of the epidemiologic studies. As discussed below, in the aggregate these studies do not demonstrate an effect of ETS on birthweight, which is consistent with the conclusion by Peacock et al. (1991a) that a threshold exists for the effect of active smoking on birthweight.

Epidemiologic studies of birthweight have used either mean

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birthweight or the incidence of intrauterine growth retardation (IGR) as the outcome measured. IGR is usually defined as low birth weight (<2500 gm) in a term (usually >36 weeks) pregnancy. Figure 1 (from MacMahon et al., 1967) illustrates the distribution of birthweights in the offspring of women who smoked during pregnancy compared to those of non-smokers. Both sets of birthweights are normally distributed, with smoking causing a shift of the curve to the left. MacMahon et al. (1966) have suggested, based on this distribution, that comparison of mean birthweights is more appropriate than comparison of the percent of offspring with birthweights less than a specific cutoff.

Most of the relevant studies on the effect of ETS on birth weight (Table 2) use paternal smoking as a surrogate for exposure. In some studies only nonsmoking women comprised the cohort, while others included both smoking and nonsmoking mothers, with the influence of maternal smoking usually being controlled for in the analysis. A group of studies published fifteen to twenty years ago, several examining large cohorts of births, did not demonstrate any effect of paternal smoking on birth weight of offspring from maternal nonsmokers, regardless of whether birth weight was considered as a continuous (mean weight) or dichotomous (incidence of low birth weight babies) parameter (Yerushalmy, 1971; Underwood, et al., 1967; MacMahon, et al., 1966; Comstock & Lundin, 1967).

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The findings of more recent studies have been inconsistent. Several studies have reported that paternal smoking is associated with decrements in mean birth weight ranging from 100 to 250 g (Borlee, et al., 1978, Karakostov, 1985; Rubin et al, 1986; Schwartz-Bickenbach, et al., 1987; Haddow et al., 1988). Additionally, Martin and Bracken (1986), studying a larger cohort of pregnant women and defining exposure as two or more hours/day of ETS exposure, found no significant effect of ETS exposure on the mean weight of offspring of nonsmoking mothers but did report an effect when birth weight was examined as a dichotomous parameter. In this study, ETS-exposed, nonsmoking women experienced an approximately two-fold increased risk of low birth weight babies (≤ 2500 g) compared to non-ETS exposed, nonsmoker women. No effect of ETS exposure occurred when the mother was a smoker rather than a nonsmoker.

On the other hand, a number of studies have found no statistically significant effects of paternal smoking or ETS exposure on birthweight (Magnus et al., 1984; Nakamura et al., 1988; Chen et al., 1989; Brooke et al., 1989; Kikuchi and Takahashi, 1990; Rantakallio et al., 1990; Lazzaroni et al., 1990 or ? 1991 -to be double-checked; Mathai et al., 1990; Ahlborg and Bodin, 1991). Ogawa et al. (1991) reported a statistically significant decrease in crude birthweight from ETS

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exposure (≥ 2 hr per day from any source) but found no dose-response relationship and no association after controlling for potential confounding factors using multiple regression analysis. MacArthur and Knox (1986) reported a statistically significant increase in birth weight from exposure to paternal smoking, after standardizing for maternal height, parity, length of gestation and sex of the infant. Mothers in this study, however, were ex-smokers who had stopped smoking early in pregnancy, requiring that the potential confounding influence of active smoking and misclassification of their current nonsmoking status be further examined.

In four of the studies cited above, including some in which no significant effect of ETS on birthweight or prevalence of low birth weight offspring was found, the data were analyzed using multiple regression analysis to adjust for the effects of potential confounding factors and to estimate the independent effect of ETS exposure. Martin and Bracken (1986) and Lazzaroni et al. (1990) reported non-statistically significant reductions in mean birthweight of 24 gm and 38 gm, respectively from ETS exposure. Rubin et al. (1986) calculated that paternal smoking was associated with a statistically significant decrease in birthweight of 6 gm/cigarette/day. Ahlborg and Bodin (1991) report a decrease in mean birthweight of 34 gm associated with ETS exposure at home and an increase in mean birthweight of 20 gm

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associated with ETS exposure at work; neither effect was statistically significant.

Taken together, the epidemiologic studies do not support the conclusion that ETS exposure affects birthweight, even after considering the potential influence of misclassification and confounding, as discussed below. Uncertainty with respect to the extent of ETS exposure can lead to both differential and non-differential bias. For example, many of the studies described above use paternal exposure as a surrogate for ETS exposure. This can result in substantial nondifferential misclassification of exposure (Friedman et al, 1983; Ogawa et al., 1991), which will tend to underestimate any effect of ETS exposure. On the other hand, in a number of studies the extent of ETS exposure, related either to paternal smoking or exposure from all sources, was estimated retrospectively, creating the possibility of differential bias. Thus, when Lazzaroni et al. (1990) found unexpectedly that the mean birthweight in offspring of women reporting greater than 5 hr/day ETS exposure was less than the mean birthweight of the offspring of women who were active smokers, they suggested that this could be related to "a possible overreporting of [ETS] exposure for women delivering newborns with low birthweight."

The use of paternal smoking as a surrogate for ETS exposure

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can introduce differential error with respect to smoking status misclassification of the mother, which will overestimate the influence of ETS exposure. This situation is analogous to that described in detail with respect to studies relating to the effect of marriage to a smoker on lung cancer risk among nonsmokers (Wald et al, 1986; Lee, 1988). Specifically, in studies examining the effects of paternal smoking on pregnancy outcome in nonsmoking women, some smokers (both married to smokers and married to nonsmokers) will, in fact, be misclassified as nonsmokers. Because smokers tend to marry smokers (concordance of smoking habits among married couples or marital aggregation) and because of the association between active maternal smoking and decreased birth weight the effect of this misclassification will impact more on the group of women married to smokers than the group married to nonsmokers. This will result in a spurious increase in the estimate of effect, totally unrelated to ETS exposure.

The precise influence of such misclassification has not been examined systematically. To do so requires data on the proportion of pregnant smoking women who will be misclassified as nonsmokers and the extent to which maternal and paternal smoking are linked. These figures should not necessarily be based on data relied upon in the lung cancer misclassification analysis. Misclassification of active smoking status may be much higher

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than that seen in the general population, given the social stigma attached to and the medical proscription of smoking during pregnancy. This is consistent with the findings of studies utilizing biomarkers to confirm self-reported nonsmoking status (Oryszczyn, 1991). There may also be a stronger correlation between maternal and paternal smoking in pregnant couples than in the general population.

A final, crucial, consideration in the evaluation of the epidemiologic studies of ETS exposure and birthweight is the influence of potential confounders. In addition to biological factors such as, sex of offspring, birth order, maternal age and parental size, environmental and lifestyle factors, including social class, nutritional status, ethanol consumption and caffeine intake have been reported independently to affect birthweight. Additionally, each of these has been associated, and in some studies shown to interact with, smoking history (e.g., Martin and Bracken, 1986; Ogawa et al., 1991; Peacock et al., 1991b; Haste et al., 1991). While the majority of the more recent studies of ETS exposure and birthweight have attempted to control for confounders, the confounders considered and the manner in which they have been handled have varied.

Rubin et al. (1986) developed what appears to be an oversimplified regression model for the influence of paternal

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smoking on birth weight. Although several confounders were considered (social class, maternal age, marital status, sex of offspring, complications, maternal alcohol consumption, and maternal smoking), each was treated in the analysis as independent rather than interacting variables. This may account for the failure of the model employed in this study to explain more than 14% of the variation in birth weight in these infants. Also, the data set in the study may not have been representative of the literature, as some commonly known factors (such as age of the mother, sex of child, parity, and alcohol intake) failed to influence birth weight.

On the other hand, Martin and Bracken (1987) concluded that most of the potential confounders they examined (maternal age, gestational age, marital status, ethnicity, education, employment, alcohol intake, caffeine intake, marijuana intake, parity, spontaneous abortions, stillbirths, weight gain during pregnancy, and body mass index) were associated with exposure to ETS and/or IGR. This suggests that ETS exposure is associated with numerous other variables that potentially can adversely affect fetal growth, underscoring how difficult it is to isolate an effect attributable to ETS with any degree of specificity.

For the most part, however, the confounders discussed above would not tend to obscure a true effect of ETS and would not

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detract from the conclusion that the epidemiologic studies reported to date do not support a finding that ETS exposure of the mother during pregnancy adversely affects the birthweight of the offspring.

The several epidemiologic studies to have examined the effect of paternal smoking or ETS exposure on pregnancy outcomes other than birthweight have reported findings that are inconsistent and questionable. Yerushalmy (1971) reported, in a cohort of over 13,000 women, that the neonatal mortality rate was elevated in low birth weight infants born to nonsmokers whose husbands were smokers. However, he also found that the mortality rate in these infants was even higher than that reported for infants born to women smokers (with or without smoker husbands). Mau and Netter (1973) also reported increased perinatal mortality in offspring of maternal nonsmokers married to smoker husbands but the lack of a dose-response relationship raises doubts about the significance of the finding. Other studies (Underwood et al., 1967; Tokuhata, 1968; Terris and Gold, 1969; Nakamura et al., 1988; Rantakallio et al., 1990; Kikuchi and Takahashi, 1990; Ahlborg and Bodin, 1991) have not found any effect of paternal smoking on perinatal mortality or prematurity.

Mau and Netter (1973) reported in a small study that the rate of malformations in offspring born to nonsmokers increased

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from a control level of 0.8% to 2.1% when fathers smoked 10 or more cigarettes a day. In a much more recent study (Seidman et al., 1990), however, no effect of paternal smoking on the incidence of malformations was found.

Genotoxic/carcinogenic risk associated with in utero exposure to ETS. ETS is a dynamic mixture of a large number of chemicals, some of which are known to be genotoxic or carcinogenic in model systems. Therefore, fetal exposure following maternal exposure to ETS involves at least a theoretically increased risk of an adverse pregnancy outcome resulting from genetic damage or an increased risk of cancer in the offspring.

In spite of this theoretical basis, neither active maternal smoking during pregnancy nor exposure to ETS during pregnancy have been demonstrated to increase the risk of cancer in offspring. Some epidemiologic studies on parental smoking and cancer risk have reported an increased risk of specific tumors or tumor incidence in general (e.g., Stjernfeldt et al., 1986; Sandler et al., 1985; Golding et al., 1990), but these studies do not distinguish between *in utero* and postnatal exposure. Furthermore, other studies do not find an effect of parental smoking on childhood cancer risk (e.g., McKinney and Stillier, 1986; Buckley et al., 1986; Schwartzbaum et al., 1991; John et

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al., 1991). Thus, at most, epidemiologic studies identify parental smoking as one of many possible risk factors for childhood cancer, but fall far short of demonstrating that parental smoking or ETS exposure causes cancer in offspring.

The susceptibility of the fetus to the genotoxic effects of tobacco smoke components may differ from that of an adult because of differences in the metabolic capability of the fetus. Many of the genotoxic/carcinogenic chemicals to which a fetus can be exposed, including those in tobacco smoke, require metabolic activation. Although, in most cases, the metabolic capability of the fetus is much less than that of an adult or even a young child, evidence exists that active smoking by the mother induces the activity of aryl hydrocarbon hydroxylase (AHH), an enzyme responsible for the activation of the polycyclic aromatic hydrocarbon (PAH) group of carcinogens. Placental AHH activity is detected almost exclusively in the placentae of smokers. However, the dose-response curve for the AHH activity as a function of the number of cigarettes smoked is sigmoidal, and the activity of the enzyme is not related to serum cotinine levels (Pasanen and Pelkonen, 1990).

Several studies have examined the influence of ETS exposure on placental AHH activity (Hincal, 1986; Manchester & Jacoby, 1981; Huel et al., 1989). Of these, Huel et al. (1989) report

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the most systematic evaluation. In this study, AHH activity was measured in placentae from active smokers, nonsmokers with ETS exposure (more than 2 cigarettes/day smoked in their presence) and nonsmokers with no ETS exposure. The relative risk for placental AHH induction was reported as 1.48 in nonsmokers with ETS exposure, compared to 1.7 in active smokers. A dose-response relationship based on the number of cigarettes smoked was reported for active smokers but was not detected in the ETS-exposed nonsmokers. These results, while suggesting increased AHH activity associated with ETS exposure, are far from conclusive. Despite the fact that urinary cotinine concentrations reported for the ETS-exposed nonsmokers suggest that there may have been significant misclassification, this possibility was not considered by the authors.

Biomarkers associated with a genotoxic effect have also been used in recent studies to assess whether tobacco smoke exposure results in genotoxic activity in the fetus. Two approaches have been used: (1) cytologic evaluation of fetal cells to quantitate the frequency of cells with evidence of chromosomal damage (i.e., by the presence of sister chromatid exchanges or micronuclei); and (2) quantitation of DNA adducts, representing the covalent binding of genotoxic chemicals to DNA. While neither of these endpoints is, in itself, an adverse health effect, each is a biomarker of genotoxic activity that, theoretically, could lead

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to an adverse health outcome.

Animal studies, involving inhalation exposure of pregnant mice to tobacco smoke, report an increase in the frequency of fetal cells with SCEs or micronuclei (Karube et al., 1989; Balansky and Blagoeva, 1989). Human data reported to date, however, do not demonstrate an *in utero* cytogenetic effect of either active smoking or ETS exposure (Sorsa and Husgafvel-Pursiainen, 1988; Sorsa et al., 1989). Active smoking -- but not exposure to ETS -- was reported to increase the frequency of cells with sister chromatid exchanges (SCE) in pregnant women but not to affect the frequency of SCEs in the fetus. Cui et al. (1990) examined chorionic villi cells from artificially aborted fetuses, and reported that paternal smoking was associated with a statistically significant increase in the frequency of cells with micronuclei. However, the validity of their findings is questionable, considering the fact that none of the 507 mothers questioned reported cigarette smoking or alcohol consumption.

The use of DNA adducts as biomarkers of carcinogenic exposure has been widely applied in recent studies, including a few studies on pregnant females and their fetuses. However, none of the studies has examined tobacco-specific adducts. In some cases the adducts appear to be tobacco-related because the

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chemical forming the adduct is known to be in tobacco smoke and is found in most smokers but not in most nonsmokers. However, it remains ^{difficult} clearly to connect the presence of the adduct with tobacco smoke exposure. Everson et al. (1986, 1988) have identified several tobacco-related DNA adducts in the placenta of active smokers but did not consider ETS exposure. More recently, Coghlin et al. (1991) reported on 4-aminobiphenyl adducts in maternal and umbilical cord blood as a function of both active smoking and exposure to ETS. Tobacco smoke exposure during the last trimester of pregnancy was quantitated through the use of a diary and a personal monitor for nicotine exposure. Adducts were found in all samples, with overlap between the amounts found in smokers and nonsmokers. This probably reflects the importance of sources of 4-aminobiphenyl other than tobacco smoke and the individual variability in the metabolic pathways leading to adduct formation. In smokers, maternal adduct levels correlated with exposure but fetal adduct levels did not. In non-smokers, no correlation between ETS exposure and adduct levels was found on the basis of the diary reports but "evidence for a positive trend" was found based on personal nicotine monitoring. However, the data supporting this conclusion have not yet been published.

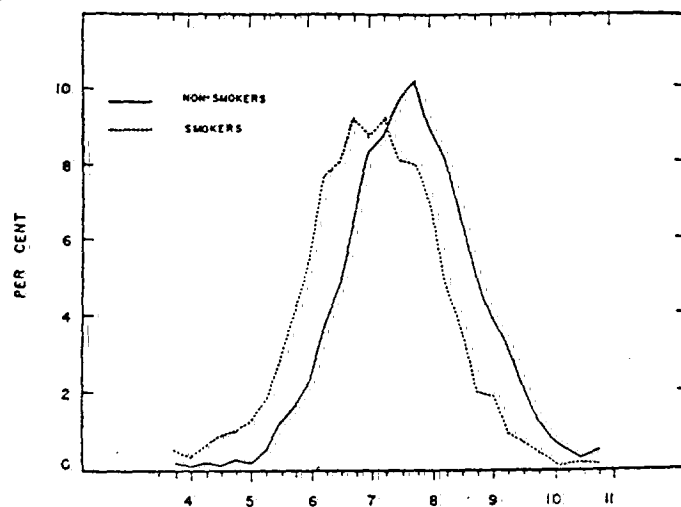
In conclusion, the foregoing discussion of epidemiologic and biomarker evidence suggests that ETS exposure does not cause a significant genotoxic or carcinogenic risk to the fetus. While

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this is a relatively new area of scientific research, the lack of convincing evidence even in active smokers renders an effect of ETS unlikely on the basis of relative dose considerations.

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Figure 1.



BIRTH WEIGHT (SCALE IN POUNDS; INTERVALS OF 4 OZS.)

FIGURE 1. Percentage distribution by birth weight of infants of mothers who did not smoke during pregnancy and of those who smoked 1 pack or more per day.

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effect in approximately equal amount over the range of environmental circumstances. Thus, table 5 shows that the difference between the weights of male and female infants bears no consistent relationship to the degree of environmental restriction imposed by birth order or maternal cigarette smoking. In fact, the group of infants in the most restricted class (first-born children of mothers smoking a pack or more per day) shows a substantially larger than average difference between mean weights of males and of females.

The fact that an effect of maternal smoking is seen in all birth order classes (table 3), but that no birth order effect is seen in the highest maternal smoking class (table 4), no doubt relates to the fact that differences in birth weight associated with maternal smoking are much greater than those associated with

birth order. Infants of mothers smoking a pack or more per day may, in fact, be experiencing close to the limit of environmental restriction of birth weight that is compatible with live birth and are consequently insensitive to other potential environmental determinants of birth weight. The sex difference seen in table 3 may be explained by supposing that the environmental restriction imposed by low birth order, although applied equally to both sexes, is, in fact, more restrictive of males because of their greater weight potential.

Since amount of maternal smoking increases with parity, it is possible that part of the trend seen in table 3 results from the fact that, within the category of smokers of a pack or more per day, women in the higher parities are smoking more heavily than those in the lower. However, consideration of the strength

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Table 2.

STUDIES EXAMINING THE EFFECTS OF ETS EXPOSURE
OR PARENTAL SMOKING ON BIRTHWEIGHT

Study	Number	Definition of Exposure	Smoking Status of Mother	Outcome Measure	Statistically Significant Findings
Comstock and Lundin, 1967	?	parental smoking	nonsmoker	mean BW	no effect
MacMahon et al, 1966	2,394	parental smoking	nonsmoker	mean BW	no effect
Underwood et al, 1967	24,865	parental smoking	nonsmoker/smoker	mean BW	no effect
Yerushalmy, 1971	?	parental smoking	nonsmoker	IGR	no effect
Borelee et al, 1978	238	parental smoking	nonsmoker	mean BW	decrease
Magnus et al, 1984	1,551	parental smoking	nonsmoker/smoker	BW	no independent effect
Karakostov, 1985	215	?	nonsmoker/exsmoker	mean BW	decrease
Martin and Bracker, 1986	2,613	≥2hr/d	nonsmoker	IGR	increased risk
Rubin et al, 1986	500	parental smoking	nonsmoker/smoker	BW	decrease (independent effect)
Schwartz-Bickelbach, 1987	54	parental smoking	nonsmoker	mean BW	decrease
MacArthur and Knox, 1987	180	parental smoking	stopped during first trimester	mean BW	increase
Hadden et al, 1988	1,230	serum cotinine ≥1ng/ml	nonsmoker	mean BW	decrease
Nakamura et al, 1988	1,444	parental smoking	nonsmoker	IGR	no effect
Chen et al, 1989	1,058	household smoking	nonsmoker	mean BW	no effect
Brooke et al, 1989	1,018	household smoking	nonsmoker	mean BW	no effect
Mathai et al, 1990	184	household smoking	nonsmoker	mean BW	no effect
Rantakallio et al, 1990	9,478	parental smoking	nonsmoker/smoker	mean BW, IGR	no effect
Kikuchi and Takahashi, 1990	778	parental smoking	nonsmoker	IGR	no effect
Lazarom et al, 1990	1,004	≥1hr exposure	nonsmoker	mean BW	no effect
Ogawa et al, 1991	5,336	≥2hr exposure	nonsmoker	BW, IGR	no independent effect
Ahlborg and Bodin, 1991	2,940	home: household smoker work: most of the time in room with smoker	nonsmoker	IGR	no effect

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